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THE PREDICTORS OF DIABETIC NEPHROPATHY IN ADULT PATIENT WITH DIABETES: SYSTEMATIC LITERATURE REVIEW

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ABSTRACT
Diabetes is a type of chronic disease that progresses over time and can lead to various complications, one of which is diabetic nephropathy. The prevalence of kidney disorders in individuals with diabetes at a productive age in Indonesia is 4%, but only 0.6% have been diagnosed. This systematic review provide information about many factors affecting diabetic nephropathy, both physical and psychological factors in adult patient with diabetes. This systematic literature review utilizes several databases, i.e EBSCO, Oxford Journal, ProQuest, PubMed, Sage Journal, Science Direct, and Springer Link which published in the past five years (2019-2024). We used PICO in literature searching process, i.e. diabetic nephropathy (population), self-care OR family support OR risk factor OR primary assessment OR early warning signs (intervention), standard care (comparison), diabetic nephropathy OR diabetic kidney disease OR glomerulosclerosis, diabetic (outcome). Articles were selected based on inclusion and exclusion criteria and are presented using the PRISMA diagram. There were 10 relevant articles were identified. The sample size in this study was 7.892 from many health care areas from primary health care, outpatient clinic, and emergency department. Diabetic patients in this study include prediabetes, type 1 diabetes, and type 2 diabetes, DM ESRD and asymptomatic severe hypertension that potential to suffer kidney disfunction. The physical factors of diabetic nephropathy were body mass index (BMI), duration of diabetes diagnosis, vital signs, laboratory examination and comorbidity. Psychological factors include family support, self-care, diabetes control and education, Quality of Life (QoL) or Well-Being Index. There were six physical factors and four psychological factors that could be predictors of diabetic nephropathy.

Keywords: diabetic nephropathy; physical factor; psychological factors

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INTRODUCTION

Diabetes mellitus is a metabolic disorder due to absolute or relative deficiency of insulin secretion or insulin resistance to its metabolic action on target cells resulting in hyperglycemia and glycosuria (Haroon and Husnain, 2021). International Diabetes Federation (IDF) reported that 10,5% population aged 20 to 79 years old suffer diabetes, but they are not aware of the condition and deaths due to diabetes reached 6.7 million in 2021 (IDF Atlas, 2021). IDF also mentioned that three of four diabetes adult patient. come from low and middle-income countries. A cohort study of non-communicable diseases in Indonesia from 2011 to 2021 stated that diabetes cause mortality (46%) and morbidity (10.5%) in the population aged over 15 years. The results of the Indonesian Health Survey stated that the prevalence of diabetes based on a doctor's diagnosis in the productive age was 1.6%, and the elderly patient was 6.5%. However, this prevalence is not in accordance with treatment and re-examination at health service facilities (Kementerian Kesehatan RI, 2023).

Diabetes requires regular treatment and management to avoid complications of the disease, such as microvascular complications. One of the microvascular complications is diabetic

nephropathy which can develop into chronic kidney disease (CKD) and end-stage renal disease (ERSD) (Skyler *et al.*, 2017). Based on combined data from 54 countries, it shows that many cases of end-stage kidney disease are caused by diabetes, hypertension, or a combination of both. The incidence of ESRD in adults with diabetes is 10 times higher than in those without diabetes. The prevalence of ESRD is highly dependent on access to dialysis and renal replacement therapy. Study about metabolic syndrome in diabetes stated that kidney disease found in 16.8% of patients. This finding is similar to that reported by de Boer et al (2020) at 15.85%, but different from the study by Thomas et al. (2022) the prevalence of diabetic nephropathy patients reached 40.8% (Asghar *et al.*, 2023). In Indonesia, prevalence of kidney disease and DM at productive age was 4% but only 0,6% have been diagnosed (Mihardja *et al.*, 2018)

The gap in the number of cases and diagnostic findings can be an indicator of the lack of compliance of DM patients with diabetes management. This can be influenced by internal patient factors or self-care. Several studies have shown that self-care can improve metabolic control, quality of life, clinical outcomes in DM patients, reduce complications and mortality, both in type 1 and type 2 DM patients (De Maria *et al.*, 2022). In contrast, inadequate diabetes self-care is associated with higher patient morbidity and mortality as well as increased costs of treatment, diagnostic tests and health care. (Kassa *et al.*, 2021). Patients with DM has a risk to develop chronic kidney disease (CKD) compared to non-diabetic patients, with odds ratios (OR) varying between 1.3 and 4.6 globally (Koye et al, 2018).

Indonesia is a multicultural country that upholds the principle of family so that patients undergoing treatment and care in hospitals. Family members have important role to provide care for diabetic nephropathy patients. Both patient and their family are essential part to maintenance healthy lifestyle and diabetes management. Study in Thailand stated that the influence of diabetes knowledge and behaviours among both elderly patients and their family caregivers on patient's Quality of Life (Thongduang *et al.*, 2022). Another study in Indonesia identified that family support as perceived by older persons in daily activities, health services, food preparation, financial support, attention, guidance, and problem solving (Kristianingrum, Wiarsih and Nursasi, 2018). There are many literature review and systematic review studies about self-care in diabetes patient, but systematic review related to physical and psychological factors in diabetic patients that have the potential risk to be diabetic nephropathy have not been widely conducted, especially in nursing reviews. This aim of this study is identifying predictor and risk factors of diabetic nephropathy, both physical assessment and psychological support, especially in primary care health care and emergency department.

METHOD

This systematic review used several databases such as EBSCO, Oxford Journal, Pro Quest, PubMed, Sage Journal, Science Direct and Springer Link. The inclusion criteria of this study are articles published in the last 5 years (2019-2024) and written in English. Study design in this study were RCT, cross sectional, and cohort study. The literature searching process used PICO and keywords are adult patient OR diabetes patient (population), self-care OR family support OR risk factor OR primary assessment OR early warning signs (intervention), standard care (comparison), diabetic nephropathy OR diabetic kidney disease OR glomerulosclerosis, diabetic (outcome). The exclusion criteria are child patients or under 18 years of age, pregnant and lactating women. The process found literature out until complete this study was conducted from August 26 to November 11, 2024. The standard protocol used is based on the selection of articles using the following Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA). The stage of extracting data has summarized the data derived from the several studies for further analysis (Diagram 1).

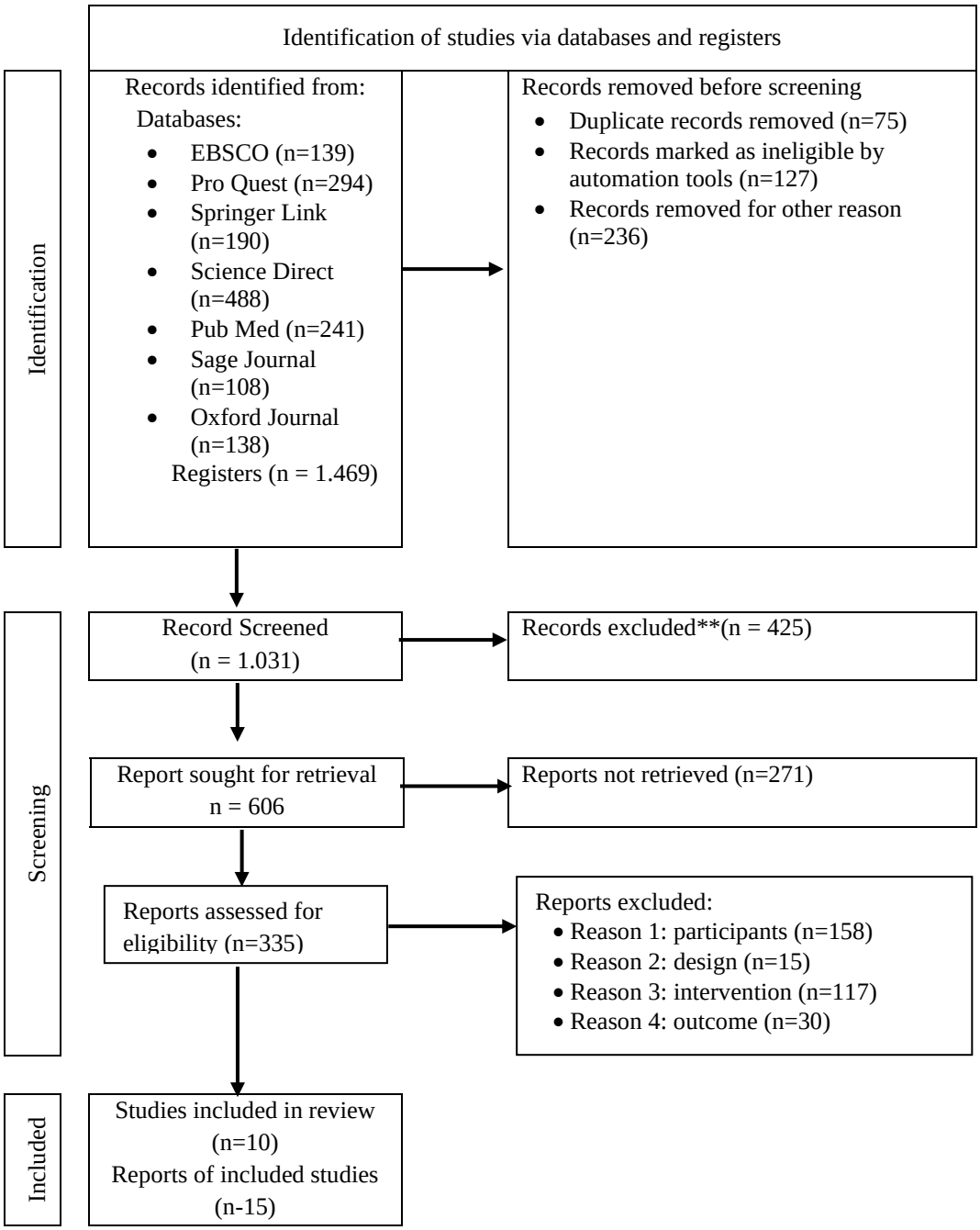

Diagram 1. PRISMA Flow Chart

RESULT

Table 1. Main Findings based on Literature

No.	Tittle	Author, Year	Research Objectives	Methods	Results
1.	Rate and risk factors of kidney function decline among South Asians with type 2 diabetes: analysis of the CARRS Trial	(Singh *et al.*, 2024)	to assess the rate and determinants of kidney function decline among type 2 diabetes patients in South Asia	Longitudinal cohort study, sample was 1146 T2DM patients in India and Pakistan	• 25% patients were showed loss eGFR (at >2 mL/min/1.73 m2 annually.

2.	Determinants of diabetes self-care activities in patients with type 2 diabetes based on self-determination theory	(Okati-Aliabad *et al.*, 2024)	to investigate self-determinant theory construct can affect the self-management and controlling HbAIc levels in type 2 DM	Cross sectional, sample 300 patients with type 2 DM	• Patients in well-being condition have good social and economic status with a mean value of self-care score (P = 0.003).
3.	Clinical utility of routine investigations and risk factors of end-organ damage in asymptomatic severe hypertension	(Ali *et al.*, 2023)	to assess the clinical utility of routine investigation and risk factors of end-organ damage in patients admitted to the emergency department with severe hypertension	Cross sectional, 180 patients in ER, Aga Khan University Hospital, Karachi, Pakistan	• Kidney was the most damaged organ (73.3%). • Patient who has history disease of DM, IHD & cerebrovascular disease has significant relationship to organ damage ($p < 0.05$).
4.	Clinical and Pharmacotherapeutic Profile of Patients with Type 2 Diabetes Mellitus Admitted to a Hospital Emergency Department	(Lopes *et al.*, 2023)	to identify the clinical and pharmacological profile of T2DM patients visiting emergency department	Retrospective study, sample 420 patients with DM type 2 in emergency department	• Family support had lower incidence of hyperglycaemia (p = 0.016). • Metformin as monotherapy or combination with DPP4 inhibitors was linked to lower incidence of AKI (p = 0.017) and CKD (p = 0.014).
5.	Prevalence and risk factors of chronic kidney disease among patients with type 2 diabetes mellitus at a tertiary care hospital in Nepal: a cross-sectional study	(Joshi *et al.*, 2023)	to assess the prevalence of CKD among patients with T2DM and identify the sociodemographic and clinical risk factors associated with CKD	Cross sectional, sample 201 DM type 2 patients above 18 years old.	• Factors that significantly influenced CKD in type 2 DM were age (p=0.026), hypertension status (p=0.002), duration of diabetes (p=0.009) and Hb value (p=0.027). There was significant relationship between CKD and literacy status.
6.	Inter-relationship of risk factors and pathways associated with chronic kidney disease in patients with type 2 diabetes mellitus: a structural equation modelling analysis	(Wang *et al.*, 2021)	to examine a hypothesis regarding causal pathways associated to CKD in patients with T2DM	prospective observational study, sample 3395 DM type 2 patients in outpatient	• Demographic data including education, marital status, mini-mental state examination score (0.075), WHO 5 well-being index (0.082) and diabetes control (0.099), HBP (0.144), triglyceride (0.091), uric acid (0.282)
7.	The differences in health-related quality of life between younger and older adults and its associated factors in patients with type 2 diabetes mellitus in Indonesia	(Sari *et al.*, 2021)	to identify the difference in HRQOL and its predictors in younger and older adults with DM in Indonesia	Cross Sectional, sample 641 DM type 2 patients from 16 Primary Health Care at Kab. Banyumas.	• 7 predictors of HRQOL in younger adults: education, job status, diabetes complications, DSM, DD, depression, self-efficacy • 4 predictors of HRQOL in older adults: income, depression, DD, self-efficacy
8.	The combined diabetes and renal control trial (C-DIRECT) - a feasibility randomised controlled trial to evaluate outcomes in multi-morbid patients with diabetes and on dialysis using a mixed	(Griva *et al.*, 2019)	• To evaluate the feasibility and acceptability of C-DIRECT. • To gather HbAIc data and patient-reported outcomes • To assess the potential effectiveness of C-	RCT, mixed methods, sample 42 patients undergoing haemodialysis with DM ESRD in dialysis centres	• C-DIRECT had higher number of participants with HbA1c < 8% at follow up compared to usual care. • Significant improvements in role limitations due to physical health were observed in the C-DIRECT group while they remained unchanged in usual care.

	methods approach		DIRECT in improving glycaemic control, psychosocial, self-care outcomes	throughout Singapore	• No statistically significant differences were found between groups for other clinical markers and other patient-reported outcomes.
9.	Early prevention of diabetes microvascular complications in people with hyperglycaemia in Europe: ePREDICE randomized trial, study protocol, recruitment and selected baseline data	(Gabriel *et al.*, 2020)	To evaluate the impact of early treatment of hyperglycaemia using antidiabetic medication combined with lifestyle intervention vs lifestyle change alone, on microvascular function in adults with pre-diabetes.	multicentre study, randomised, clinical trial. Sample 908 patients from primary care centres in 9 countries	• Prevalence of diabetic nephropathy was 5.7%. • ePREDICE sample represent well the adult pre-diabetic population who use public primary care services across Europe.
10.	Lower Blood Oxygen Saturation is Associated with Microvascular Complications in Individuals with Type 1 Diabetes	(Laursen *et al.*, 2023)	To investigate whether hypoxemia is linked to the presence of diabetic complications in Type 1 DM	Cross sectional, sample 659 patients in Steno Diabetes Center Copenhagen, Herlev, Denmark	• SpO2 level below 96% was linked to higher prevalence of albuminuria. • The adjusted odds ratio (95% CI, P value) for low versus high SpO2 was 3.4 (1.3- 8.7, P=0.01) for albuminuria in DM type 1

Systematic Review Results

Overall, 863 out of 1.469 articles screened by title and abstract were excluded, leaving 606 for full text review. When the full text of papers was screened, a total of 271 studies were excluded primarily due to lack of relevance to the aim of this study. From the remaining 335 studies, 15 studies specifically focus on patient with a diabetes diagnosed who developed microvascular complication such as diabetic nephropathy. Ultimately, 10 out of 15 articles were selected for further analysis in this study. The sample size in this study was 7.892 from various health care settings, including primary health care, outpatient clinic, and emergency department. Diabetic patients in this study consisted of pre-diabetes (10%), type 1 diabetes (10%), type 2 diabetes (60%), DM ESRD (10%) and the remaining were emergency patients with asymptomatic severe hypertension that potentially leading to kidney disfunction. The aim is to determine whether the type of diabetes can influence microvascular complications, particularly in the kidneys. All these diabetic patients have the potential to progress to diabetic nephropathy (Table 1).

Hypoxia occurs in the kidneys of patients with type 1 and type 2 DM. Study in type 1 DM showed that SpO2 level below 96% was linked to higher prevalence of albuminuria. The number of patients who had albuminuria was 23% (Laursen *et al.*, 2023). Study in type 2 DM patients showed that mostly (80%) had decreased of kidney function (Singh *et al.*, 2024) and the prevalence of CKD in type 2 DM was 86.6% (Okati-Aliabad *et al.*, 2024). Factors that significantly influenced CKD in type 2 DM were age (p=0.026), hypertension status (p=0.002), duration of diabetes (p=0.009) and Hb value (p=0.027). Differences of age could be divided into younger adult and older adults. There were seven predictors of HRQOL in younger adults including level of education, occupation status, diabetes complications, Diabetes Self-Management, Diabetes Distress, depression, and self-efficacy. In older adults, there were four predictors of HRQOL, depression, DD, and self-efficacy (Wang *et al.*, 2021)

Risk of Bias

Critical appraisal in this study used Joanna Briggs Institute (JBI) instrument for observational study and Cochrane Risk of Bias Tool for RCT. JBI takes a distinct perspective on what constitutes evidence, and the methodologies employed to synthesise various types of evidence. Consistent with comprehensive approach, JBI has formulated theories, methodologies and rigorous processes for the critical appraisal and synthesis of these diverse forms of evidence in order to support clinical decision-making in healthcare (JBI, 2020). The JBI score ranged at 63,6% to 100% to assess risk of bias in this study. The higher score indicates the methodological suitability based on the JBI checklist means low risk of bias. Unlike the JBI checklist, Cochrane Risk of Bias Tool consist of domain and description to assess high risk of bias, low risk of bias and unclear risk of bias directly. The result of critical appraisaprocess, two articles that used Randomized Control Trial design in this study has low risk of bias.

Table 2.
Predictors mentioned in Literature

No	Author, Year	Physical Factors						Psychological Factors			
		BMI	Duration of diabates	Comorbidy	Renal test	HbAIc, glycemia	Vital sign	QoL / well-being	Diabetes Control / Education	Self-care	Family support
1.	(Singh *et al.*, 2024)	√	√	√	√	√	X	√	√	X	X
2.	(Okati-Aliabad *et al.*, 2024)	X	√	√	X	√	X	X	X	√	X
3.	(Ali *et al.*, 2023)	X	X	√	√	√	√	X	X	X	X
4.	(Lopes *et al.*, 2023)	X	X	√	√	√	X	X	√	√	√
5.	(Joshi *et al.*, 2023)	√	√	√	√	√	√	X	X	X	X
6.	(Wang *et al.*, 2021)	√	√	X	√	√	√	√	√	√	X
7.	(Sari *et al.*, 2021)	√	√	√	X	√	√	√	√	√	√
8.	(Griva *et al.*, 2019)	X	√	√	X	√	X	√	√	√	√
9.	(Gabriel *et al.*, 2020)	√	X	√	√	√	√	X	√	X	X
10.	(Laursen *et al.*, 2023)	√	√	√	√	√	√	X	X	X	X

DISCUSSION

The number of patients with diabetes mellitus (DM) increased in Indonesia and got seventh ranks in the world (IDF, 2019). Type 2 DM has a high risk both of microvascular and macrovascular complications. As many as 25-35% of patients suffer from nephropathy which can develop into chronic kidney disease (Slieker *et al.*, 2021). Decreased kidney function can also occur in type 1 DM patients, which is characterized by albuminuria in 23% of patients.

(Laursen *et al.*, 2023). Therefore, nurses need to identify factors related to nephropathy in DM, especially in emergency services and primary care. Based on 10 articles that have been found, the author divides them into physical and psychosocial factors.

1. Physical Factors

Hypoxia occurs in the kidneys of patients with type 1 and type 2 DM. Hypoxia in the renal tubules is a major driver of tubular atrophy and interstitial fibrosis. This condition caused further worsen glomerular pathology when the progression of diabetic nephropathy. Renal tubular hypoxia is primarily caused by increased oxygen consumption due to increased flux through the Sodium-glucose cotransporter and increased respiratory leakage induced by mitochondrial uncoupling. Tubular hypoxia drives expansion of the extracellular matrix, resulting in further reduction in oxygen delivery and initiating a self-perpetuating cycle that contributes to the development of diabetic nephropathy (Catrina and Zheng, 2021). Hypoxia in the kidneys is not always indicated by peripheral oxygen saturation results. In a study of patients with type 1 diabetes, it was found that patients who showed low SpO2 were only 3.5% and the remaining 96.5% showed high SpO2. After further analysis, microvascular complications was albuminuria (Laursen *et al.*, 2023). Other studies have shown that hypertension disease factors (p=0.002), length of diagnosis (p=0.009) and hemoglobin values (p=0.027) significantly affect CKD in type 2 DM. Identification of CKD-EPI is known from the eGFR value with a median value of 83.6 (IQR: 67.7 - 97.9) mL/min/1.73 m2 and a mean eGFR value = −1.33/mL/min/1.73 m2/year. Most of patients of the study showed decline of kidney function while a quarter of patients were experiencing rapid eGFR loss (at >2 mL/min/1.73 m2 annually (Singh *et al.*, 2024). Other factors are blood creatinine values, glycemic index values, hyperuricemia, ACS disease and types of drugs consumed. Metformin consumed as monotherapy or together with DPP4 inhibitor was associated with a lower incidence of AKI (p = 0.017) or CKD (p = 0.014) (Joshi et al, 2023; Lopes et al, 2023; Singh et al, 2024). This strengthens the results of previous research which stated that hypertension, triglycerides, and uric acid have a direct effect on CKD. (Wang et al, 2021). Studies related to clinical factors in Indonesia Health Center mentioned BMI, length of diagnosis, smoking history, hypertension, complications, glycemic index and types of DM treatment. The Physical Component Summary (PCS) includes physical function, body pain, general appearance, role limitations due to health problems in young adults (18-64 years) shows a greater value than in older adults (Sari et al, 2021).

2. Psychosocial Factors

Nurses provide services not only focusing on the clinical aspects of patients, but also psychosocial aspects to support better health. Psychosocial factors found in this literature search include family support. Patients with family support showed fewer incidences of hyperglycemia (p = 0.016) and self-care. The average value of self-care activities = 34.62 ± 11.86 with a maximum value of 70. Patients in the fourth quadrant (well-being) have good social and economic status (Lopes et al, 2023; Okati-Aliabad et al., 2024). This is relevant to previous research in Taiwan which stated that demographic data including level of education, marital status and MMSe (mini-mental state examination), (p=0.075), WHO 5 well-being index (p=0.082), diabetes control (0.099) had a significant relationship with the risk of CKD (Wang et al, 2021). Studies related to diabetes distress reported an average age of 58 years and 21% were female. The average HbA1c was 9.8%, and 37.5% had moderate to high levels of diabetes distress (DD), higher baseline HbA1c and Personal Health Questionnaire-8 (PHQ-8) scores were associated with higher total DD. Higher PHQ-8 was associated with higher interpersonal distress. Higher HbA1c and higher PHQ-8 scores were associated with higher regimen-related distress. Higher basal insulin used and PHQ-8 were associated with higher

physician-related distress. Higher PHQ-8 scores were associated with higher emotional burden (German et al, 2023). A study at the Indonesian Health Center that analyzed the relationship between the Mental Component Summary (MCS) variable and the quality of life of diabetes patients showed that no significant differences were found in young and older adults. MCS includes social function, fighting spirit/spirit, mental health and role limitations due to emotional problems. Education level, employment status, Diabetes Self-Management (DSM), Diabetes Distress (DD), depression, and self-efficacy are factors that significantly influence HRQOL in young adults. (Sari et al, 2021).

CONCLUSION

There are factors influencing the development of diabetic nephropathy complications, which include clinical and psychological factors, as identified from various references. Clinical factors Body Mass Index (BMI), duration of diabetes diagnosis, comorbidities, vital signs especially blood pressure and oxygen saturation, laboratory results to measure renal function test, HbA1c, and glycemic index. Psychological factors include quality of life or well-being family support, self-care, diabetes control and education, Quality of Life (QoL) or WHO-5 Well-Being Index. The strength of this study is large sample size, representing diverse characteristics of diabetic patients at risk of diabetic nephropathy complications, especially in primary care and emergency settings. However, a limitation of this study is the predominance of observational studies due to the limited availability of interventional research on diabetic nephropathy. Consequently, there is a need for intervention-based research applicable to healthcare settings.

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